The Oncologist®

Clinical Trial Results

# Anlotinib Combined with S-1 in Third- or Later-Line Stage IV Non-Small Cell Lung Cancer Treatment: A Phase II Clinical Trial

Miao Xiang,[a] Xiyue Yang,[a] Surong Ren,[a] Huan Du,[b] Lidan Geng,[a] Li Yuan,[a] Yixue Wen,[a] Binwei Lin,[a] Jie Li,[a] Yu Zhang, Gang Feng,[a] Xiaobo Du [a]

[a]Department of Oncology, Mianyang Central Hospital, Mian Yang, People's Republic of China; [b]Department of Oncology, Affiliated Hospital of North Sichuan Medical College, Nan Chong, People's Republic of China

*Miao Xiang, Xiyuei Yang, and Surong Ren are co-first authors.

**Key Words.** Non-small cell lung cancer • Anlotinib • S-1 • Third-line treatment

## Trial Information

- **Trial ID**: Chinese Clinical Trial Registry (Number: ChiCTR 1900020948)
- **Sponsor**: Beijing Bethune Charitable Foundation (B19136DT)
- **Principal Investigator**: Xiaobo Du
- **IRB Approved**: Yes

## Lessons Learned

- The combination of anlotinib and S-1 exhibited good antitumor activity in third- or later-line treatment for stage IV non-small cell lung cancer (NSCLC).
- Combination therapy of anlotinib with S-1 has manageable toxicities in patients with NSCLC.

## Abstract

***Background.*** This study aimed to evaluate the efficacy and safety of anlotinib combined with S-1 as a third- or later-line treatment for patients with stage IV non-small cell lung cancer (NSCLC). Anlotinib was approved in 2018 by the Chinese Food and Drug Administration (FDA) as a third-line treatment for patients with refractory advanced NSCLC and is under study in the U.S. and Europe.

***Methods.*** Simon's phase II clinical trial design with an $\alpha$ error of 5% and a power $\beta$ of 80% was used, anticipating a 10% objective response rate (ORR) of anlotinib and a 30% ORR of anlotinib combined with S-1; the required sample size was 29. A total of 29 patients were enrolled in the clinical trial. Patients were treated with anlotinib plus S-1 over a 21-day treatment course until disease progression or unacceptable toxic effects. If the efficacy was assessed as stable disease, partial response, or complete response after six cycles, anlotinib was maintained until disease progression or death. The primary endpoint was the objective response rate. Somatic mutations were not required for study enrollment.

***Results.*** The median follow-up time was 11.1 months. Objective responses were observed in 11 of 29 (37.9%) patients making up the intention-to-treat population, which reached the target primary endpoint of 30% ORR. The median overall and progression-free survival were 16.7 and 5.8 months, respectively. The most common grade 3 adverse events (AEs) were gastrointestinal, including nausea, vomiting and diarrhea, fatigue, and hypertension. No grade 4 treatment-related AEs or treatment-related deaths occurred.

***Conclusion.*** The combination of anlotinib with S-1 in the third- or later-line treatment of stage IV NSCLC shows promising antitumor activity and manageable toxicity in patients with NSCLC; phase III trials will be planned in the future. ***The Oncologist*** 2021;26:e2130–e2135

Correspondence: Xiaobo Du, M.D., Department of Oncology, Mianyang Central Hospital, Changjiaxiang #12, MianYang, Sichuan, People's Republic of China 621000. Telephone: 86-08162217667; e-mail: duxiaobo2005@126.com Received May 7, 2021; accepted for publication August 14, 2021; published Online First on September 13, 2021.  http://dx.doi.org/10.1002/onco.13950

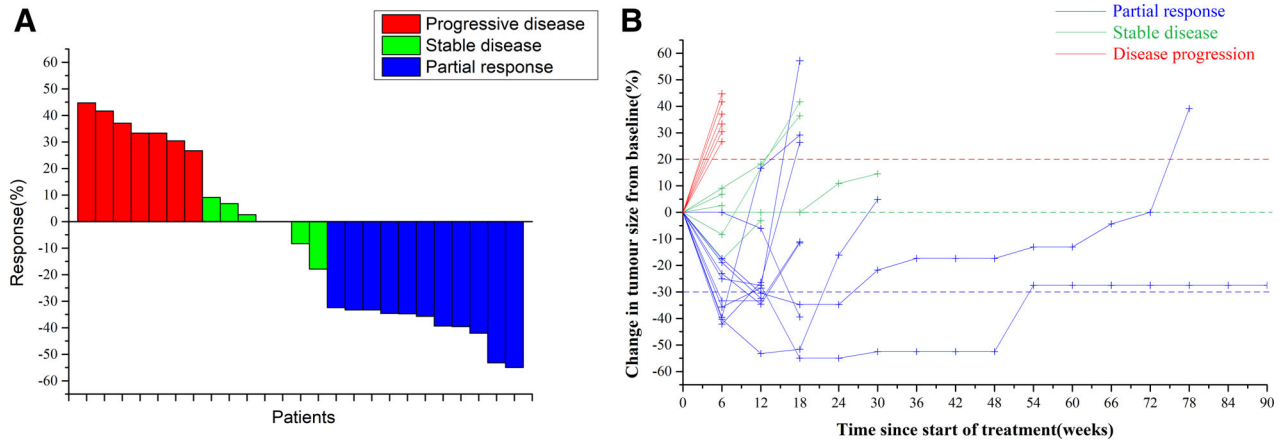


**Figure 1. (A):** Waterfall plot for maximal percentage change in target lesion size. **(B):** Line chart of changes in the tumor size.

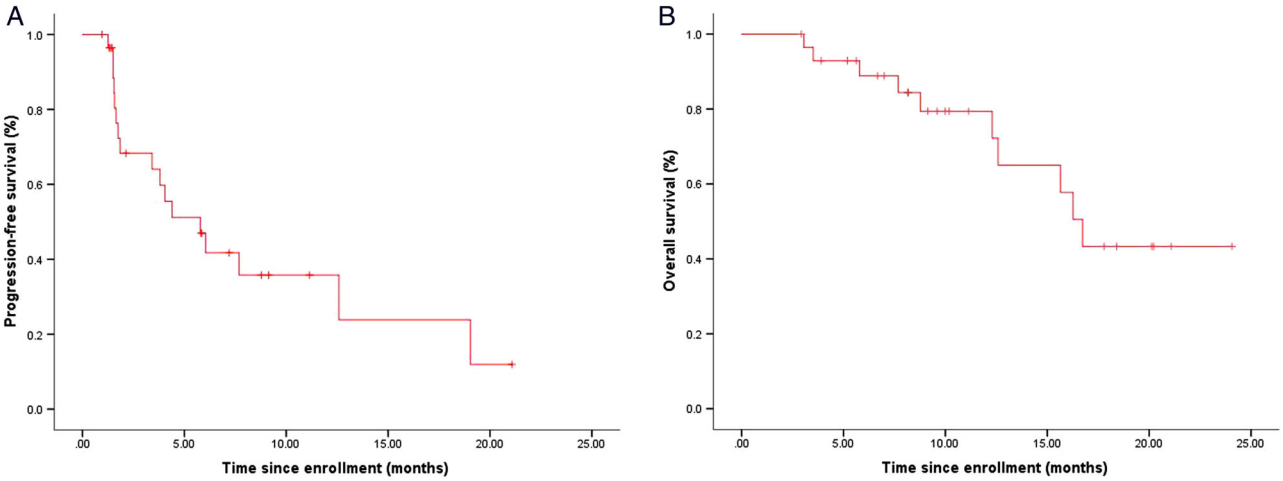


**Figure 2.** Kaplan-Meier curves of overall survival **(A)** and progression-free survival **(B)**.

## Discussion

Anlotinib is an oral, multitargeted tyrosine kinase (TK) receptor inhibitor, which was more effective than placebo in third-line treatment of patients with advanced NSCLC. However, the ORR was only 9.2% and the overall survival (OS) time was prolonged only 3 months. In the U.S., ramucirumab is most similar to anlotinib, but it was not approved by the Chinese FDA for the treatment of NSCLC. The combination of multitargeted TK receptor inhibitors and chemotherapy is effective and well tolerated in patients with NSCLC and ovarian cancer. Therefore, we hypothesized that anlotinib combined with chemotherapy may be an effective treatment strategy for patients with stage IV NSCLC, leading to the present study combining anlotinib with S-1. Oral S-1 is a third-generation fluorouracil derivative, with good efficacy and relatively low toxicity in the treatment of stage IV NSCLC.

This prospective study reached the target primary endpoint of 30% ORR; the ORR was 37.9%, and the disease control rate (DCR) was 62.1% in the 29 patients who participated in the study. Excluding four (13.8%) patients who did not undergo postbaseline evaluation because of adverse reactions, the ORR was 44%, and the DCR was 72% in 25 patients who had at least one postbaseline evaluation. The secondary endpoints were as follows: median progression-free survival was 5.8 months and median overall survival was 16.7 months. The patient who achieved the best response (55% reduction by RECIST) also had the longest treatment time among all patients. The patient continued to show >30% decline from the baseline for 36 weeks. These results indicated that the combination of anlotinib and S-1 exhibited good antitumor activity in third-line or above treatment for stage IV NSCLC (Figs. 1 and 2).

The most common grade 3 adverse events (AEs) were gastrointestinal (3 [10.3%]), fatigue (2 [6.9%]), and hypertension (2 [6.9%]). Most of the AEs were reversible. In addition, no grade 4 treatment-related AEs or deaths were recorded. The toxicity was controllable, and the combination therapy did not significantly increase the adverse reactions.

Notably, both anlotinib and S-1 are orally administered without the need for hospital admission or an infusion pump, which may improve patient compliance and reduce economic costs. In conclusion, the current study showed that the combination therapy of anlotinib with S-1 has promising efficacy and manageable toxicities in patients with NSCLC, supporting planned phase III trials.

| Trial Information | |
|---|---|
| **Disease** | Lung cancer - NSCLC |
| **Stage of Disease/Treatment** | Metastatic/advanced |
| **Prior Therapy** | More than two prior regimens |
| **Type of Study – 1** | Phase II |
| **Type of Study – 2** | Single arm |
| **Primary Endpoint** | Overall response rate |
| **Secondary Endpoint** | Progression-free survival, safety |

**Additional Details of Endpoints or Study Design**

***Study design*:** This phase II, single-arm, prospective clinical trial was approved by the Ethics Committee of Mianyang Central Hospital, Sichuan, China (Number: S2019001) and was conducted according to the tenets of the Declaration of Helsinki and its later amendments. All participants provided written informed consent prior to participation. The study was registered at the Chinese Clinical Trial Registry (Number: ChiCTR1900020948), and its detailed rationale and methods have been published elsewhere [11]. Briefly, we enrolled patients with cytologically or histologically confirmed stage IV NSCLCfrom Mianyang Central Hospital in Sichuan province. The eligibility criteria were the following: (a) age 18–75 years; (b) pathologically diagnosed with stage IV NSCLC; (c) Eastern Cooperative Oncology Group performance status score 0–2 points; (d) disease progression after at least one line of chemotherapy and tyrosine kinase inhibitor therapy for patients with positive driver mutations epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement and at least two lines of chemotherapy for patients tested negative for driver mutations; (e) a measurable lesion based on the RECIST 1.1 criteria; (f) expected survival time ≥ 12 weeks; (g) normally functioning major organs.

***Dosage regimen*:** Anlotinib: 12 mg, once daily, administered orally for 2 weeks on/1 week off over a 21-day treatment course, until disease progression or unacceptable toxic effects. S-1: 70 mg/m$^2$, twice a day, administered orally for 2 weeks on/1 week off, over a 21-day treatment course, for a maximum of six cycles. If the efficacies were assessed as stable disease, partial response, or complete response after six cycles, anlotinib was maintained until disease progression or death.

***Efficacy and safety assessments*:** The primary endpoint was ORR, and the secondary endpoints were DCR, progression-free survival (PFS), overall survival (OS), and safety. The treatment effect was assessed every two cycles by measuring the target lesions via computed tomography imaging. Tumor response was assessed according to the RECIST 1.1. The evaluation of adverse reactions was based on the guidelines of National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.

***Statistical analysis*:** We used Simon's phase II clinical trial design with an $\alpha$ error of 5% and a power $\beta$ of 80%, given a 10% ORR of anlotinib, and an anticipated 30% ORR of anlotinib combined S-1, and estimated the required sample size as 29 cases. The 30% ORR of anlotinib combined S-1 is the target primary endpoint of the study. SPSS 22.0 statistical software (IBM, Armonk, NY) was used to analyze the data collected by the cutoff date of January 11, 2021. The ORR was calculated using the Clopper-Pearson method. The ORRs with different clinical characteristics were compared using $\chi^2$ test. Multivariate analysis of the independent prognostic factors was performed using the Cox regression model. A log-rank test was applied to evaluate the differences in PFS and OS between groups. The Kaplan-Meier method was used to assess PFS and OS with 95% confidence intervals (CIs). Origin 9.0 software was used to draw waterfall and line charts. Two-sided values of $p \leq .05$ were considered statistically significant.

| | |
|---|---|
| **Investigator's Analysis** | Active and should be pursued further |

| Drug Information | |
|---|---|
| **Generic Name** | Anlotinib |
| **Trade Name** | Anlotinib |
| **Company Name** | Chia Tai Tianqing Pharmaceutical Co. Ltd |
| **Drug Type** | Small molecule |
| **Drug Class** | VEGFR |
| **Dose** | 12 mg per flat dose |
| **Route** | p.o. |
| **Schedule of Administration** | 12 mg, once daily, administered orally for 2 weeks on/1 week off over a 21-day treatment course, until disease progression or unacceptable toxic effects. If the efficacy in any given patient was assessed as stable disease, partial response, or complete response after six cycles, anlotinib was maintained until disease progression or death. |
| **Generic Name** | S-1 |
| **Trade Name** | S-1 |
| **Company Name** | Lunan Pharmaceutical Group |
| **Drug Type** | Biological |
| **Drug Class** | Antimetabolite |

| | |
|---|---|
| **Dose** | 70 mg/m$^2$ |
| **Route** | p.o. |
| **Schedule of Administration** | 70 mg/m$^2$, twice a day, oral for 2 weeks on/1 week off, 21 days as a course of treatment, until disease progression or unacceptable toxic effects, for a maximum of six cycles. |

| Patient Characteristics | |
|---|---|
| **Number of Patients, Male** | 24 |
| **Number of Patients, Female** | 5 |
| **Stage** | IV |
| **Age** | Median: 58 years |
| **Number of Prior Systemic Therapies** | Median (range): 2 (2–5) |
| **Performance Status: ECOG** | 0 — 10<br>1 — 9<br>2 — 10<br>3 —0<br>Unknown —0 |
| **Cancer Types or Histologic Subtypes** | Adenocarcinoma, 22<br>Squamous, 5<br>Adenosquamous, 2 |

| Primary Assessment Method | |
|---|---|
| **Title** | Objective response rate |
| **Number of Patients Screened** | 29 |
| **Number of Patients Enrolled** | 29 |
| **Number of Patients Evaluable for Toxicity** | 29 |
| **Number of Patients Evaluated for Efficacy** | 25 |
| **Evaluation Method** | RECIST 1.1 |
| **Response Assessment CR** | $n = 0$ (0%) |
| **Response Assessment PR** | $n = 11$ (37.90%) |
| **Response Assessment SD** | $n = 7$ (24.05%) |
| **Response Assessment PD** | $n = 7$ (24.05%) |
| **(Median) Duration Assessments PFS** | 5.8 months, CI: 95% CI: 2.9–8.7 |
| **(Median) Duration Assessments OS** | 16.7 days, CI: 95% CI: 14.9–18.6 |

**Adverse Events**

**All Dose Levels, All Cycles**

| Name | NC/NA | 1 | 2 | 3 | 4 | 5 | All grades |
|---|---|---|---|---|---|---|---|
| Fatigue | 45 | 34 | 14 | 7 | 0 | 0 | 55 |
| Hemorrhage, pulmonary/upper respiratory | 83 | 10 | 3 | 3 | 0 | 0 | 17 |
| Hypertension | 62 | 21 | 10 | 7 | 0 | 0 | 38 |
| Nausea | 64 | 18 | 7 | 11 | 0 | 0 | 36 |
| Liver dysfunction/failure (clinical) | 66 | 28 | 7 | 0 | 0 | 0 | 34 |
| Proteinuria | 83 | 14 | 3 | 0 | 0 | 0 | 17 |
| Rash: hand-foot skin reaction | 79 | 7 | 7 | 7 | 0 | 0 | 21 |
| Rash: acne/acneiform | 93 | 3 | 3 | 0 | 0 | 0 | 7 |
| Hypothyroidism | 69 | 17 | 14 | 0 | 0 | 0 | 31 |

All data are presented as %.
Toxicities during treatment ($n = 29$).
Abbreviation: NC/NA, no change from baseline/no adverse event.

| Assessment, Analysis, and Discussion | |
|---|---|
| **Completion** | Study completed |
| **Investigator's Assessment** | Active and should be pursued further |

Lung cancer is the second leading cause of cancer-related morbidity and the leading cause of mortality worldwide, with an estimated 2.2 million new lung cancer cases and 1.8 million deaths in 2020 [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 85% of lung cancer [2], and most of the newly diagnosed patients present with metastatic disease [3]. Targeted therapy and immunotherapy play a critical role in the treatment of advanced NSCLC. However, drug resistance in the late stage of targeted therapy is a major concern, and because of its high cost, immunotherapy may not be available. Therefore, third-line treatment has become a key area of research after the failure of second-line chemotherapy or targeted drug therapy for patients with advanced NSCLC.

Tumor angiogenesis has been identified as a critical therapeutic target for a malignant tumor, and vascular endothelial growth factor and its receptors are involved in the core signaling pathway in angiogenesis-related molecular mechanisms. Anlotinib is a new oral small-molecule tyrosine kinase inhibitor that has a broad spectrum of inhibitory actions against tumor growth and angiogenesis [4, 5]. The ALTER-0303 [6] trial showed that anlotinib was more effective than placebo in the third-line treatment of patients with advanced NSCLC. Compared with the placebo group, the objective response rate (ORR) and disease control rate (DCR) of the patients in the anlotinib group were improved (ORR 9.18% vs. 0.7%, $p < .0001$; DCR 80.95% vs. 37.06%, $p < .0001$). In addition, anlotinib significantly prolonged the median PFS and OS compared with the placebo group (PFS 5.37 vs. 1.40 months, $p < .0001$; OS 9.63 vs. 6.30 months, $p < .0001$). Based on the ALTER-0303 study, the Chinese Society of Clinical Oncology guidelines recommended anlotinib as the standard third-line treatment for advanced NSCLC [7]. However, the ORR was only 9.18% and the OS time was prolonged by only 3 months.

The combination of multitargeted tyrosine kinase receptor inhibitors and chemotherapy is effective and well tolerated in patients with NSCLC and ovarian cancer [8, 9], suggesting that anlotinib combined with chemotherapy could be an effective treatment strategy for patients with stage IV NSCLC. S-1 is an oral fluoropyrimidine formulation with high antitumor activity as a third-line therapy for NSCLC. Nokihara et al. [10] reported that S-1 had an ORR of 19% when used as a third-line treatment for NSCLC. Ono et al. [11] reported the use of S-1 as a third- or fourth-line therapy for NSCLC, with an ORR of 5.7% in a retrospective analysis. A previous study reported [12] that when S-1 was used as third-line therapy, PFS was 3.3 months, and OS was 12.2 months. S-1 is also well tolerated in elderly patients [13]. Oral S-1 is a cost-effective treatment option for patients with advanced NSCLC. However, the response rate of a single drug does not demonstrate sufficient activity for patients with advanced NSCLC.

At present, the effective rate of third-line treatment for advanced NSCLC is low, and there are few effective options in the clinical setting. Both anlotinib and S-1 are oral antitumor drugs and are more convenient for patients. They have proven efficacy in patients with third- and later-line advanced NSCLC and good safety. One retrospective study [14] demonstrated that the combination of S-1 and anlotinib prolonged OS compared with the anlotinib group ($8.07 \pm 0.56$ vs. $6.17 \pm 0.42$ months), but no significant change was observed in PFS between the two groups ($3.87 \pm 0.29$ months vs. $3.00 \pm 0.24$ months). The ORR (20.0% vs. 10.0%) and DCR (75.0% vs. 60.0%) of the combined therapy group were significantly higher than those of the anlotinib single group, but the difference was not statistically significant.

This prospective study reached the target primary endpoint of 30% ORR; the ORR was 37.9% (95% CI: 20.7–57.7), and the DCR was 62.1% (95% CI: 42.3–79.3) in the 29 patients who participated in the study. Excluding 4 (13.8%) patients who did not undergo postbaseline evaluation because of adverse reactions, the ORR was 44% (95% CI: 24.4–65.1), and the DCR was 72% (95% CI: 50.6–87.9) in 25 patients who had at least one postbaseline evaluation. The secondary endpoints were as follows: median progression-free survival was 5.8 (95% CI: 2.9–8.7) months, and the median overall survival was 16.7 (95% CI: 14.9–18.6) months. In contrast, the patient who achieved the best ORR (55%) also had the longest treatment time among all patients. The patient continued to show >30% decline from the baseline for 36 weeks. These results indicated that the combination of anlotinib and S-1 exhibited good antitumor activity in third-line or above treatment for stage IV NSCLC. This prospective study achieved a better outcome than the retrospective study noted above [14]. We consider this likely to be due to the synergistic effect of anlotinib and chemotherapy.

Common adverse events (AEs) were fatigue, myelosuppression, gastrointestinal reaction, and hypertension. The common grade 3 AEs were gastrointestinal reaction (3 [10.3%]), fatigue (2 [6.9%]), and hypertension (2 [6.9%]). Most of the AEs were reversible. In addition, no grade 4 treatment-related AEs or deaths were recorded. The toxicity was controllable, and the combination therapy did not significantly increase the adverse reactions.

Both anlotinib and S-1 are orally administered without the need for hospital admission or an infusion pump, which may improve patient compliance and reduce economic costs.

Nevertheless, the present study had some limitations. First, it was a single-arm study with no randomized control design, and hence, selection bias could not be ruled out. Second, the sample size of this study was small and recruited from a single institution. Third, at the beginning of the study, we did not evaluate the indicators, such as smoking status, brain metastasis, and previous treatment regimen, which might be related to the therapeutic effect.

In conclusion, the current study showed that the combination therapy of anlotinib with S-1 has promising efficacy

and manageable toxicities in patients with NSCLC, indicating a need for phase III trials.

## Disclosures

The authors indicated no financial relationships.

## References


**1.** Sung H, Ferlay J, Siegel RL et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2021;71:209–249.

**2.** Ettinger DS, Akerley W, Borghaei H et al. Non-small cell lung cancer. J Natl Compr Canc Netw 2012;10:1236–1271.

**3.** Miller KD, Siegel RL, Lin CC et al. Cancer treatment and survivorship statistics, 2016. CA Cancer J Clin 2016;66:271–289.

**4.** Lu J, Zhong H, Chu T et al. Role of anlotinib-induced CCL2 decrease in anti-angiogenesis and response prediction for nonsmall cell lung cancer therapy. Eur Respir J 2019;53:1801562.

**5.** Lin B, Song X, Yang D et al. Anlotinib inhibits angiogenesis via suppressing the activation of VEGFR2, PDGFRbeta and FGFR1. Gene 2018;654: 77–86.

**6.** Han B, Li K, Wang Q et al. Third-line treatment: A randomized, double-blind, placebo-controlled phase III ALTER-0303 study—efficacy and safety of anlotinib treatment in patients with refractory advanced NSCLC. J ClinOncol 2017;35 (suppl 15):9053.

**7.** Zhou M, Chen X, Zhang H et al. China National Medical Products Administration approval summary: Anlotinib for the treatment of advanced non-small cell lung cancer after two lines of chemotherapy. Cancer Commun (Lond) 2019;39:36.

**8.** Nishio M, Horai T, Horiike A et al. Phase 1 study of lenvatinib combined with carboplatin and paclitaxel in patients with non-small-cell lung cancer. Br J Cancer 2013;109:538–544.

**9.** Chun-Yan L, Yin W, Ying X et al. Apatinib combined with oral etoposide in patients with platinum-resistant or platinum-refractory ovarian cancer (AEROC): A phase 2, single-arm, prospective study. Lancet Oncol 2018;19:1239–1246.

**10.** Nokihara H, Nagai S, Kato T et al. Phase II study of S-1 in non-small cell lung cancer (NSCLC) patients previously treated with a platinum-based regimen. J Thorac Oncol 2007; 2(suppl 8):S687.

**11.** Ono A, Naito T, Murakami H et al. Evaluation of S-1 as third- or further-line chemotherapy in advanced non-small-cell lung cancer. Int J Clin Oncol 2010;15:161–165.

**12.** Ikezawa Y, Asahina H, Oizumi S et al. A randomized phase II trial of erlotinib vs. S-1 as a third- or fourth-line therapy for patients with wild-type EGFR non-small cell lung cancer (HOT1002). Cancer Chemother Pharmacol 2017; 80:955–963.

**13.** Imai H, Minemura H, Kishikawa T et al. Efficacy and safety of S-1 monotherapy in previously treated elderly patients (aged ≥75 years) with non-small cell lung cancer: A retrospective analysis. Thorac Cancer 2020;11:2867–2876.

**14.** Xie XH, Wang F, Lin XQ et al. Anlotinib plus S-1 for patients with EGFR mutation-negative advanced squamous cell lung cancer with PS scores of 2-3 after progression of second-line or later-line treatment. Cancer Manag Res 2020;12: 12709–12714.